201-14277A

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN

FOR

2-CHLOROPYRIDINE

CAS NO. – 109-09-1

PREPARED BY:

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OVERVIEW

Arch Chemicals, Inc. (Arch) hereby submits for review and public comment the test plan for 2-chloropyridine (2-PCl; CAS # 109-09-1) under the Environmental Protection Agency's High Production Volume Chemical Challenge Program. It is the intent of Arch to use existing data, data proposed under the test plan and estimated values using predictive computer models acceptable to EPA to adequately fulfill the Screening Information Data Set (SIDS) for the physical/chemical endpoints, environmental fate, ecotoxicity and human health-related toxicology.

2-PCl is a colorless, oily liquid used as an intermediate in synthetic organic, pharmaceutical and agricultural chemical manufacture. It is a key intermediate in the manufacture of pyrithione-based biocides for use in cosmetics and various pharmaceutical products. It is also used as a starting material in the production of the antihistamine drug, pheniramine and the antiarrhythmic drug, diisopyramide. This chemical is not sold to the individual consumer. Its uses are in the industrial workplace where exposures are tightly controlled.

TEST PLAN SUMMARY

2-Chloropyridine CAS # 109-09-1	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	-	Y	N	Y	N
Boiling Point	Y	-	-	Y	N	Y	N
Vapor Pressure	Y	-	-	Y	N	Y	N
Partition Coefficient	Y	-	-	Y	N	Y	N
Water Solubility	Y	-	-	Y	N	Y	N
ENVIRONMENTAL FATE DATA							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	N	-	-	-	-	-	N
Biodegradation	Y	N	Y	N	N	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICOLOGICAL DATA							
Acute Toxicity to Fish	Y	-	-	Y	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	-	-	Y	N	Y	N
Toxicity to Aquatic Plants	Y	-	-	Y	N	Y	N
MAMMALIAN TOXICOLOGICAL DATA							
Acute Toxicity	Y	N	-	-	N	Y	N
Repeated Dose Toxicity	N	-	-	-	-	-	Y
Genetic Toxicity							
Mutation	Y	N	Y	-	N	Y	N
Chromosomal Aberration	Y	N	Y	-	N	Y	N
Developmental Toxicity	N	-	-	-	-	-	Y
Toxicity to Reproduction	N	-	-	-	-	-	Y

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physical/Chemical Endpoints

Melting Point – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Boiling Point – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.) and from a reliable reference text. The entry from the reference text (Sax and Lewis, 1987) is the preferred value.

Vapor Pressure – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Partition Coefficient – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.) and from a reliable reference text. The entry from the reference text (Hansch et al., 1995) is the preferred value.

Water Solubility – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.) and from a reliable reference text. The entry from the reference text (CRC Handbook of Chemistry and Physics, 1995) is the preferred value.

Conclusion – All endpoints have been satisfied by the utilization of data obtained from the various physical/chemical data modeling programs or reliable reference texts as referenced above. The results from the utilization of these computer modeling programs are recognized by EPA as acceptable in lieu of actual data or values obtained from literature references. Thus, no new testing is needed in the area of physical/chemical properties.

B. Environmental Fate Endpoints

Photodegradation – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Stability in Water – Although hydrolysis can not be predicted using a computer estimation model, 2-chloropyridine does not have a site in which the water molecule or hydroxide ion can displace an atom or group of atoms. Chemical hydrolysis at a pH normally found in the environment, i.e. 5 to 9, can be important for a variety of chemicals that have functional groups that are potentially hydrolysable, such as amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters.

Biodegradation – This endpoint was satisfied using studies to assess degradation in both anaerobic (3 studies) and aerobic (2 studies) systems. There was not one study that could be singled out as the key study. They all indicate that 2-

chloropyridine is resistant to biodegradation. In the aerobic system 1-10% was degraded in 24-64 days. In the anaerobic system no significant biodegradation was detected. Therefore, the 5 studies should be taken as a package to indicate that 2-chloropyridine is resistant to biodegradation.

Fugacity – A value for this endpoint was obtained using the EPIWIN Level III portioning computer estimation model (EPIWIN, Version 3.10.).

Conclusion – All endpoints have been satisfied using actual data, through the use of EPA-acceptable estimation models, or, in the case of stability in water, scientific judgment to support the position for testing requirements. No additional testing is needed in the area of environmental fate.

C. Ecotoxicity Endpoints

Acute Toxicity to Fish – A value for this endpoint was obtained using a computer program for estimating the ecotoxicity of industrial chemicals based on structure-activity relationships (Nabholz et al., 2001).

Acute Toxicity to Aquatic Invertebrates – A value for this endpoint was obtained using a computer program for estimating the ecotoxicity of industrial chemicals based on structure-activity relationships (Nabholz et al., 2001).

Toxicity to Aquatic Plants – A value for this endpoint was obtained using a computer program for estimating the ecotoxicity of industrial chemicals based on structure-activity relationships (Nabholz et al., 2001).

Conclusion – All endpoints have been satisfied through the use of EPA-acceptable estimation models. No additional testing is needed in the area of ecotoxicity.

D. Mammalian Toxicological Endpoints

Acute Toxicity – The studies that satisfy this endpoint were conducted prior to introduction of GLP. However, all studies (oral LD_{50}, dermal LD_{50} and inhalation LC_{50}) to define the acute toxicological profile were conducted in accordance with currently accepted scientific principles and are considered reliable. Two studies were conducted to define the acute dermal toxicity. The study by Gehring et al. (1967) is the key study because it determined a specific dermal LD_{50} value contrasted with the study by Wazeter (1964) in which the LD_{50} was characterized as less than an observed value. Two studies were conducted to define the acute inhalation toxicity. The study by Gehring et al. (1967) is the key study because it defined the LC_{50} value between two concentrations contrasted with the study by Wazeter (1964) in which the LC_{50} was characterized as less than an observed value.

Repeat Dose Toxicity – This endpoint has not been satisfied. A study will be conducted to address this endpoint and will conform to OECD guidelines (OECD 407) and will be conducted according to GLP guidelines.

Genetic Toxicity

Mutation (bacterial) – This endpoint has been satisfied with an Ames/*Salmonella* reverse mutation bacterial assay using strains TA97, TA98, TA100 and TA102 of *Salmonella typhimurium.* This study is reliable and is comparable to a guideline study (OECD 471).

Mutation (mammalian, *in vitro*) – Since the Ames assay indicates that 2-chloropyridine is positive, the OECD SIDS guidelines suggest a mammalian gene mutation assay be conducted. This endpoint was satisfied with a forward mutation assay using heterozygous L5178Y $TK^{+/-}$ -3.7.2C mouse lymphoma cells. This study is reliable and was conducted according to accepted scientific principles.

Chromosomal aberration (mammalian, *in vitro*) – This endpoint was evaluated as a component of the study to assess point mutation in heterozygous L5178Y $TK^{+/-}$ -3.7.2C mouse lymphoma cells. The cells were evaluated for chromosomal aberrations and micronuclei.

Developmental Toxicity – This endpoint has not been satisfied. A study will be conducted to address this endpoint and will conform to OECD guidelines (OECD 421) and will be conducted according to GLP guidelines.

Reproductive Toxicity – This endpoint has not been satisfied. A study will be conducted to address this endpoint and will conform to OECD guidelines (OECD 421) and will be conducted according to GLP guidelines.

Conclusion – The endpoints for acute toxicity and genetic toxicity have been satisfied with data from studies that were conducted utilizing methods that are similar to established guidelines and are scientifically appropriate. The endpoints of repeat dose toxicity, reproductive toxicity and developmental toxicity have not been satisfied. Studies will be conducted to supply data for these endpoints and they will be conducted according to OECD guidelines and GLP assurances.

SIDS DATA SUMMARY

Data to assess the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility) for 2-chloropyridine were obtained from EPA-acceptable computer estimation modeling programs found in EPIWIN. These data indicate that 2-chloropyridine is a liquid at room temperature with a low vapor pressure. It has a low estimated octanol to water partition coefficient and is moderately soluble in water. The use of these modeled data meet the requirements of the various endpoints and thus there is no need for any additional testing to determine physicochemical properties.

Data to address endpoints for environmental fate of photodegradation, biodegradation and fugacity were obtained from actual studies or EPA-acceptable computer estimation modeling programs found in EPIWIN. As a result of its solubility in water and relatively low volatility, fugacity estimations predict that 2-chloropyridine will distribute primarily to soil and water. Computer modeling predicts that 2-PCl will slowly degrade in the atmosphere. Actual testing using aerobic and anaerobic systems indicates that 2-PCl is resistant to biodegradation. The computer modeling program can not estimate the rate constants for aqueous base/acid-catalyzed hydrolysis. Although hydrolysis cannot be predicted using a computer estimation model, 2-chloropyridine does not have a site in which the water molecule or hydroxide ion can displace an atom or group of atoms. Chemical hydrolysis at a pH normally found in the environment, i.e. 5 to 9, can be important for a variety of chemicals that have functional groups that are potentially hydrolysable, such as amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters. It is the position of Arch Chemicals that data for this endpoint is not necessary since this chemical does not possess a structure that is hydrolysable. The judgment is that 2-PCl would be resistant to acid/base-catalyzed hydrolysis.

The data for aquatic toxicity endpoints were obtained from EPA-acceptable computer estimation modeling programs found in ECOSAR (Nabholz et al., 2001). 2-Chloropyridine is of moderate toxicity to fish, daphnids and algae. The LC_{50} to fish (96 hours) and *Daphnia* (48 hours) is 277 mg/l and 286 mg/l, respectively. The EC_{50} (96 hours) to algae is 173 mg/l.

The data to determine acute toxicity and genetic toxicity are from studies that were conducted according to acceptable scientific methodology. The inhalation LC_{50} (4 hours) is between 100 and 250 ppm. The oral LD_{50} and dermal LD_{50} are 342 mg/kg and 64 mg/kg, respectively. 2-Chloropyridine induces mutations in two separate *in vitro* systems, the Ames/*Salmonella* assay (Claxton et al., 1987) and in a mammalian assay using mouse lymphoma (L5178Y) cells (Dearfield et al., 1993). Dearfield et al. (1993) also found 2-chloropyridine to be clastogenic as demonstrated by increases in chromosome aberrations and micronuclei. Based on the results of the mutagenicity assays, 2-chloropyridine is classified as a mutagen.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the systematic approach described by Klimisch et al. (1997). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. They are:

1. Reliable without restriction: Includes studies or data complying with Good Laboratory Practices (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

2. Reliable with restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

3. Not reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

4. Not assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

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